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09/559,344	04/27/2000	Claude Negrier	06478.1442	2949

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EXAMINER
SCHNIZER, HOLLY G

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1653	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No. 09/559,344	Applicant(s) NEGRIER ET AL.	
	Examiner Holly Schnizer	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 April 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

1. The Amendment filed February 27, 2002 has been entered and considered. Claims 8-14 have been added. Therefore, Claims 1-14 are pending.

Drawings

2. The drawings have been approved by the draftsperson.

Rejections Withdrawn

3. The rejection of Claim 1 as indefinite under 35 U.S.C. 112, second paragraph for recitation of "DNA coding for a promoter" is withdrawn in light of the amendment to the claims.

4. The rejection of Claims 3 and 4 under 35 U.S.C. 112, second paragraph for insufficient antecedent basis for "the cDNA"(clm. 3) and "the first truncated intron"(clm. 4) is withdrawn in light of the amendment.

5. The rejection of Claim 4 as indefinite under 35 U.S.C. 112, second paragraph for the recitation of "inserted additionally into the FIX-cDNA" without indicating what, if anything, else was inserted is withdrawn in light of the amendment.

6. The rejection of Claims 5-7 as indefinite under 35 U.S.C. 112, second paragraph because the relationship between the Factor IX that is expressed and the DNA construct that is transfected is unclear is withdrawn in light of the amendment to the claim.

7. The rejection of Claim 4 under 35 U.S.C. 103(a) as being unpatentable over Hao et al. and Uzan et al. as applied to claim 1, and further in view of Kurachi et al. (J. Biol. Chem. (1995) 270(10): 5276-5281; cited in IDS of Paper No. 2) is withdrawn in view of the amendment to claim 8 , from which it depends, that limits the hematopoietic cells to platelets. Neither Hao et al. nor Uzan et al. teach or suggest recombinant expression specifically in platelets.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2 and new Claim 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As explained in the previous Office Action (Paper No. 5), the phrase "DNA coding for the human platelet glycoprotein IIb" is unclear (see p. 2, line 2 of paragraph numbered 3 in the Office Action). The phrase "wherein the DNA sequence functions as a promoter" implies that a promoter is being described. However, the phrase that follows; "DNA coding for the human platelet glycoprotein IIb" implies a DNA sequence coding for the protein. Thus, the claim is confusing as to whether the DNA construct contains a DNA sequence coding for a human platelet glycoprotein IIb or a DNA sequence that is the human platelet glycoprotein IIb promoter. Clarification is required.

Therefore, the rejection of Claim 2 is maintained. Newly added Claim 12 is also rejected for the reasons described above. Clarification is required.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 1, 5, and new claims 9 and 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hao et al. (Human Gene Therapy (July 1995) 6: 873-880) in view of Uzan et al. (J. Biol. Chem. (1991) 266(14): 8932-8939).

2. The rejection is restated below followed by a response to Applicants arguments.

3. Hao et al. teaches a DNA construct for the expression of factor IX in a hematopoietic cell line (HL-60 cells; p. 877, Col. 2) comprising DNA coding for a blood

coagulation factor (FIX) and a process of using the construct to express factor IX in a hematopoietic cell line (HL-60; see abstract). Hao et al. suggests using hematopoietic-specific promoters (p. 879, Col. 1, lines 27-28). Hao et al. also teaches induction of expression with PMA (clm 5-7) in HL-60 cells (p. 878, Table I).

4. Hao et al. does not teach specifically using the GPIIb promoter but does suggest using hematopoietic specific promoters to express factor IX in general.

5. Uzan et al. provides a characterization of the GPIIb promoter and concludes that the GPIIb promoter contains sufficient information to direct tissue specific expression and suggests that this promoter can be used to target expression of heterologous genes in megakaryocytes (hematopoietic cells; see p. 8932, 1st paragraph of intro. And p. 8938, Col. 2, last two lines).

6. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the DNA construct for the expression of factor IX as taught in Hao et al. such that it contained the hematopoietic specific promoter, GPIIb, characterized in Uzan et al. and use the DNA construct in a method of making factor IX as taught in Hao et al. One would have been motivated to make such a DNA construct and use it to produce Factor IX because Hao et al. teaches that DNA constructs comprising a hematopoietic-specific promoter and a sequence coding for Factor IX are desirable for potential use in transfecting hematopoietic cells to be used in the treatment of hemophilia because they are more readily obtained than other cells, such as hepatocytes (see p. 878, Discussion, paragraph bridging Col. 1 and 2). Thus, it appears that the claims are unpatentable over the prior art.

Applicants argument that the amount of factor IX produced by the different constructs of Hao et al.shown in Table I demonstrate that not all promoters direct the construct to the HL-60 cells such that factor IX can be produced and that the production levels of factor IX are low has been considered but is not deemed to be persuasive for the following reasons: Applicant appears to be arguing against the references individually and one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The ultimate goal of the Hao et al. research is to engineer a cell to produce and secrete sufficient levels of a functional clotting factor that could act as a continuous in vivo source. As part of this research, Hao et al. show that successful expression of factor IX in a hematopoietic cell line can be achieved using the Moloney murine leukemia virus long terminal repeat (vector LIXSN) or the cytomegalovirus promoter (vector LIXCIX) (see paragraph spanning p. 877-888 and Table I). Hao et al. suggests improving on this success using hematopoietic specific promoters (see p. 878, Col. 2, last paragraph and p. 879, Col. 1, first paragraph, and p. 879, Col. 1, lines 27-28). In addition, Uzan et al. teach that the GPIIb promoter directs tissue specific expression in megakaryocytes. Thus, one of ordinary skill in the art at the time of the invention having the Hao et al. and Uzan et al. references in hand would have had a reasonable expectation of success. Moreover, with Hao et al. suggestion to use hematopoietic specific promoters in the production of factor IX, one of skill in the art

would have been motivated to use the GPIIb promoter taught in Uzan et al. because it was shown to be specific for megakaryocytes.

Applicant's argument that Hao et al. does not know what type of hematopoietic cell to use and that Hao et al. does not suggest using megakaryocytes is not persuasive because the claims are not drawn and thus not limited to a particular hematopoietic cell. Moreover, again Applicant appears to be arguing against the references individually and one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. . See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants argument that Hao et al. is unsure whether expression of factor IX in primary cells will work even if a hematopoietic specific promoter were used is not persuasive because the claims are not limited to expression in primary cells. Moreover, Applicants have not provided any evidence to support the argument that one of skill in the art would believe that there is an unreasonable expectation of success in expressing factor IX in primary cells using the teachings of Hao et al. and Uzan et al. In this case, Applicant is reminded that the only examples provided in the present specification are drawn to *in vitro* expression.

7. Applicants argument that Uzan et al. only discloses use of the GPIIb promoter in megakaryocytes and not in phagocytes, lymphocytes, or erythrocytes has been considered but is not persuasive for the following reasons. Applicant appears to be arguing against the references individually and one cannot show nonobviousness by

attacking references individually where the rejections are based on combinations of references. . See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As previously stated, Hao et al. teaches that DNA constructs comprising a hematopoietic-specific promoter and a sequence coding for Factor IX are desirable for potential use in transfecting hematopoietic cells to be used in the treatment of hemophilia because they are more readily obtained than other cells, such as hepatocytes (see p. 878, Discussion, paragraph bridging Col. 1 and 2). It is noted here that the examiner did not find any suggestion by Hao et al. as to the particular hematopoietic cell line to use. Hao et al. describe "[t]he use of the erythroid-specific promoter from the β-globin gene has been shown to direct globin exclusively to the mature erythrocyte" (p. 879, Col. 1, lines 19-21) as an example of successful tissue specific expression and then suggest that hematopoietic specific promoters also could be used to provide persistent expression in vivo (p. 879, Col. 1, lines 27-28).

8. Thus, for the reasons stated above, the claims appear to be unpatentable over Hao et al. in view of Uzan et al.

New Rejections Necessitated by Amendment

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-4, 8, 13, and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8, 13, and 14 are indefinite because platelets are not hematopoietic cells and thus the claim is improperly dependent. Platelets are cytoplasmic fragments of megakaryocytes and do not contain a nucleus.

Claims 2-4 are indefinite since they depend from Claims 8, 13, and 14 and do not correct the deficiency. Correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-4, 8, 13, and 14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors are summarized in In re Wands (858 F2d, 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include (1) quantity of experimentation, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples,

(4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The nature of the Invention and Predictability or Unpredictability of the Art.

New Claims have been added that are directed to a DNA construct for the tissue specific expression of blood coagulation factors in platelets. Claims 5 and 9 include the step of transfecting hematopoietic cells and Claims 13 and 14, which depend from Claims 9 and 5, respectively, indicate that the hematopoietic cells are platelets. Thus, the claims involve direct recombinant expression in platelets. Platelets are cytoplasmic fragments of megakaryocytes and do not contain a nucleus. DNA expression requires transcription of the DNA into mRNA and then translation of the mRNA into protein. Transcription occurs in the nucleus of a cell. Thus, it appears that platelets would not support expression of transfected DNA because platelets do not contain a nucleus. And, it would be predictable that blood coagulation factors could not be recombinantly expressed, as claimed, in platelets.

The Amount of direction or guidance presented only involves in vitro expression of factor IX in megakaryocytes.

The specification does not teach or provide any guidance as to how to use a DNA-construct specific for expression in platelets or any guidance as to how blood proteins can be recombinantly expressed directly in platelets.

There are no working examples of using DNA constructs for the tissue specific expression of blood proteins in platelets.

The specification only provides working examples of DNA constructs comprising DNA encoding Factor IX operably linked to the human platelet glycoprotein IIb (GPIIb) promoter and methods of producing Factor IX in Human Erythroleukemia (HEL) cells (indicated on page 5, first paragraph of the specification as being classical cell line used to test megakaryocytic promoter expression) *in vitro* using this construct.

State of the Prior Art and Relative Skill of those in the Art

As evidenced in the obviousness rejection above, those of skill in the art would recognize that a DNA construct comprising the sequence coding for Factor IX operably linked to the GPIIb promoter could be used for tissue specific expression in megakaryocytes. However, it is common knowledge in the art that platelets do not have a nucleus, that a nucleus is required for expression, and thus that platelets could not be used to support recombinant expression.

Quantity of Experimentation

The quantity of experimentation required to obtain successful recombinant expression of a blood factor in platelets is undue because platelets do not contain the cellular machinery required for expression as explained above.

Thus, for the reasons cited above, the specification is not considered to be enabling for one of skill in the art to make and/or use the claimed invention.

Conclusions

No Claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Mon. & Thurs., 8am-5:30pm and Tues. & Wed. 9-2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

Holly Schnizer
May 11, 2002

CHRISTOPHER S. F. LOW
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